

thereafter, as long as the therapy continues.

(c) *Patient package insert contents.* A patient package insert for an estrogen drug product is required to contain the following information:

- (1) The name of the drug.
- (2) The name and place of business of the manufacturer, packer, or distributor.
- (3) A statement regarding the benefits and proper uses of estrogens.
- (4) The contraindications to use, i.e., when estrogens should not be used.
- (5) A description of the most serious risks associated with the use of estrogens.
- (6) A brief summary of other side effects of estrogens.
- (7) Instructions on how a patient may reduce the risks of estrogen use.
- (8) The date, identified as such, of the most recent revision of the patient package insert.

(d) *Guidance language.* The Food and Drug Administration issues informal labeling guidance texts under §10.90(b)(9) of this chapter to provide assistance in meeting the requirements of paragraph (c) of this section. Requests for a copy of the guidance text should be directed to the Center for Drug Evaluation and Research, Division of Metabolism and Endocrine Drug Products (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(e) *Exemptions.* This section does not apply to estrogen-progestogen oral contraceptives. Labeling requirements for these products are set forth in §310.501.

(f) *Requirement to supplement approved application.* Holders of approved applications for estrogen drug products that are subject to the requirements of this section must submit supplements under §314.70(c) of this chapter to provide for the labeling required by paragraph (a) of this section. Such labeling may be put into use without advance approval by the Food and Drug Administration.

[55 FR 18723, May 4, 1990]

**§310.517 Labeling for oral hypoglycemic drugs of the sulfonylurea class.**

(a) The University Group Diabetes Program clinical trial has reported an

association between the administration of tolbutamide and increased cardiovascular mortality. The Food and Drug Administration has concluded that this reported association provides adequate basis for a warning in the labeling. In view of the similarities in chemical structure and mode of action, the Food and Drug Administration also believes it is prudent from a safety standpoint to consider that the possible increased risk of cardiovascular mortality from tolbutamide applies to all other sulfonylurea drugs as well. Therefore, the labeling for oral hypoglycemic drugs of the sulfonylurea class shall include a warning concerning the possible increased risk of cardiovascular mortality associated with such use, as set forth in paragraph (b) of this section.

(b) Labeling for oral hypoglycemic drugs of the sulfonylurea class shall include in boldface type at the beginning of the "Warnings" section of the labeling the following statement:

**SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY**

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19 (supp. 2): 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of (name of drug) and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this

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study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

[49 FR 14331, Apr. 11, 1984]

### § 310.518 Drug products containing iron or iron salts.

Drug products containing elemental iron or iron salts as an active ingredient in solid oral dosage form, e.g., tablets or capsules shall meet the following requirements:

(a) *Labeling.* (1) The label of any drug in solid oral dosage form (e.g., tablets or capsules) that contains iron or iron salts for use as an iron source shall bear the following statement:

WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

(2)(i) The warning statement required by paragraph (a)(1) of this section shall appear prominently and conspicuously on the information panel of the immediate container label.

(ii) If a drug product is packaged in unit-dose packaging, and if the immediate container bears labeling but not a label, the warning statement required by paragraph (a)(1) of this section shall appear prominently and conspicuously on the immediate container labeling in a way that maximizes the likelihood that the warning is intact until all of the dosage units to which it applies are used.

(3) Where the immediate container is not the retail package, the warning statement required by paragraph (a)(1) of this section shall also appear prominently and conspicuously on the information panel of the retail package label.

(4) The warning statement shall appear on any labeling that contains warnings.

(5) The warning statement required by paragraph (a)(1) of this section shall be set off in a box by use of hairlines.

(b) The iron-containing inert tablets supplied in monthly packages of oral contraceptives are categorically ex-

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empt from the requirements of paragraph (a) of this section.

[68 FR 59715, Oct. 17, 2003]

### § 310.519 Drug products marketed as over-the-counter (OTC) daytime sedatives.

(a) Antihistamines, bromides, and scopolamine compounds, either singly or in combinations, have been marketed as ingredients in over-the-counter (OTC) drug products for use as daytime sedatives. The following claims have been made for daytime sedative products: “occasional simple nervous tension,” “nervous irritability,” “nervous tension headache,” “simple nervousness due to common every day overwork and fatigue,” “a relaxed feeling,” “calming down and relaxing,” “gently soothe away the tension,” “calmative,” “resolving that irritability that ruins your day,” “helps you relax,” “restlessness,” “when you’re under occasional stress . . . helps you work relaxed.” Based on evidence presently available, there are no ingredients that can be generally recognized as safe and effective for use as OTC daytime sedatives.

(b) Any OTC drug product that is labeled, represented, or promoted as an OTC daytime sedative (or any similar or related indication) is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted as an OTC daytime sedative (or any similar or related indication) is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Any OTC daytime sedative drug product introduced into interstate commerce after December 24, 1979, that is not in compliance with this section is subject to regulatory action.

[44 FR 36380, June 22, 1979; 45 FR 47422, July 15, 1980, as amended at 55 FR 11579, Mar. 29, 1990]